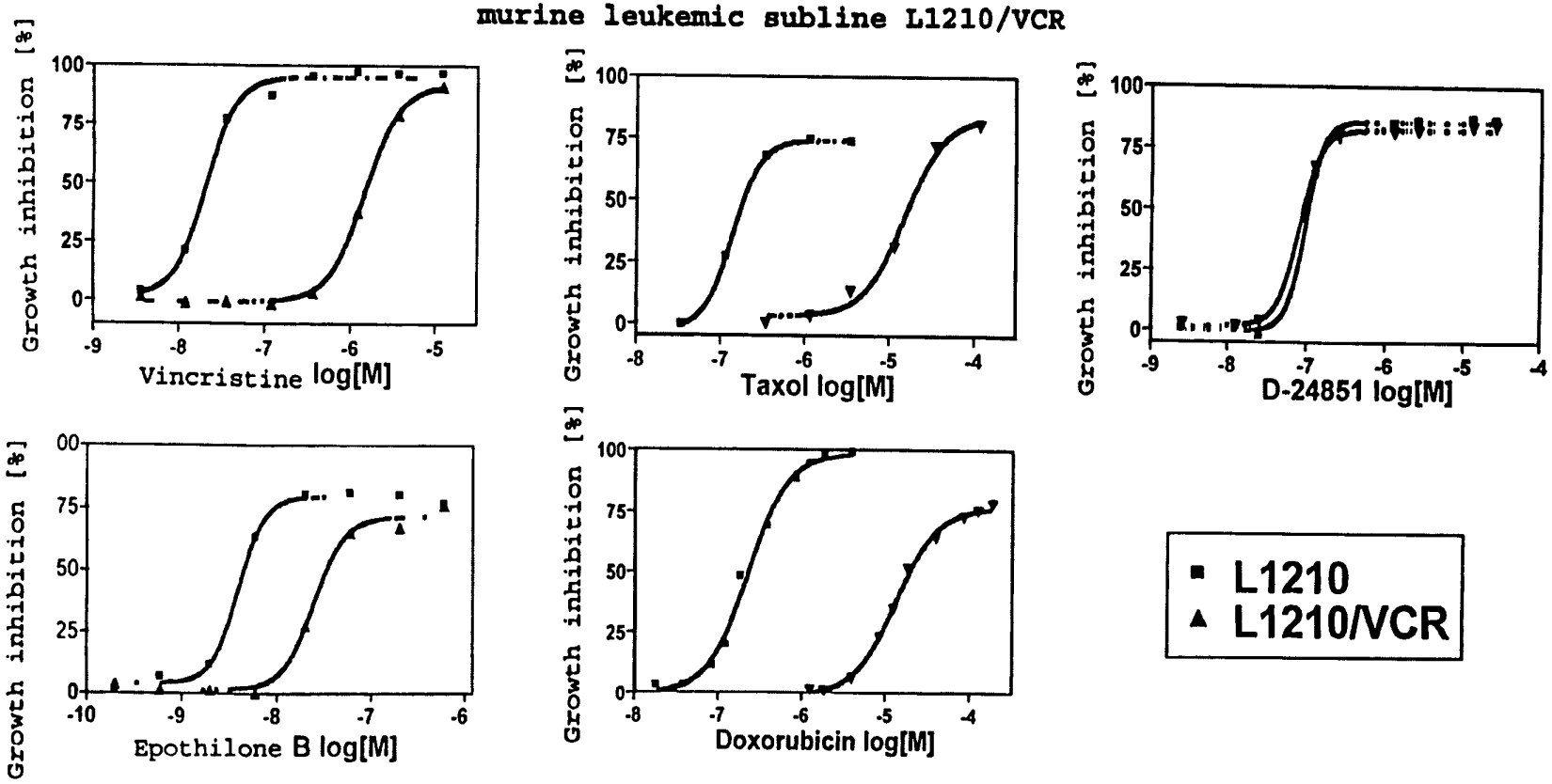
Cytotoxic action of D-24851 against MDR murine leukemic subline L1210/VCR



- In contrast to Taxol, doxorubicin, vincristine or epothilone B, D-24851 has the same cytotoxic activity against the MDR mouse leukemic subline L1210/VCR as against the normal LL1210

FIG. 1

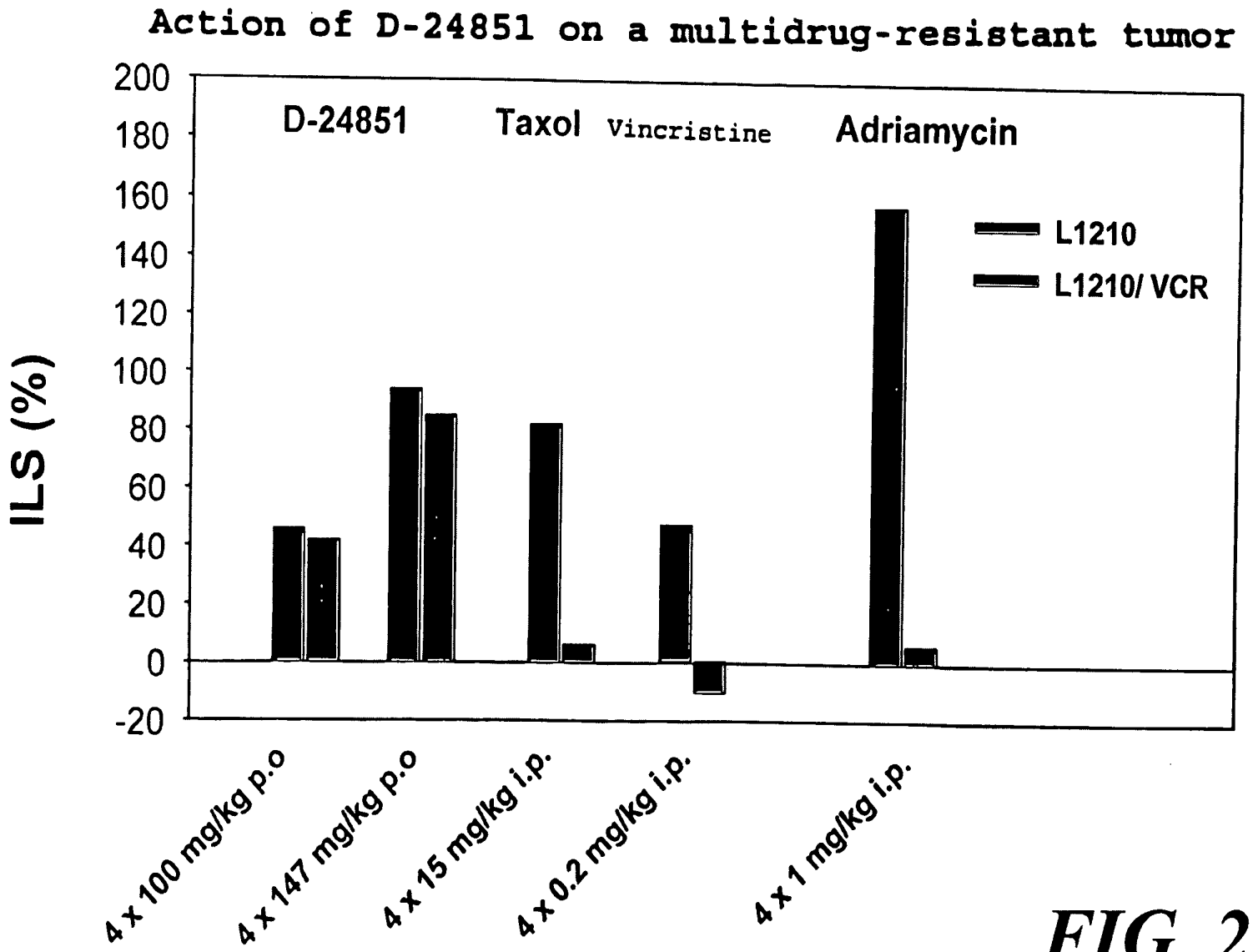

Action of D-24851 on a multidrug-resistant tumor
ILS (%)
200
180
160
140
120
100
80
60
40
20
0
-20
D-24851
Taxol
Vincristine
Adriamycin
L1210
L1210/ VCR
4 x 100 mg/kg p.o
4 x 147 mg/kg p.o
4 x 15 mg/kg i.p.
4 x 0.2 mg/kg i.p.
4 x 1 mg/kg i.p.

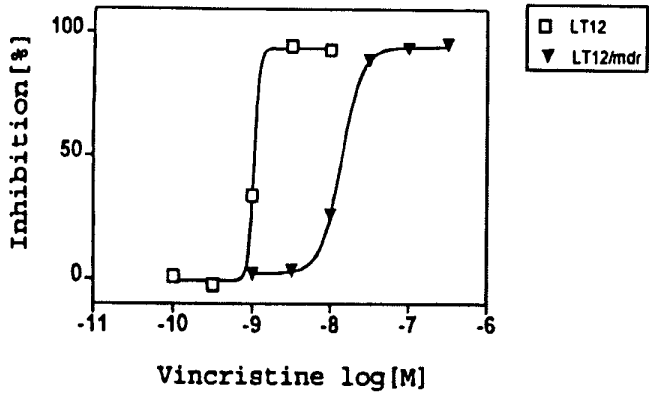
FIG. 2

Influence of D-24851 on the multidrug-resistant murine leukemia L1210 (dose 10% of the LD_{50})

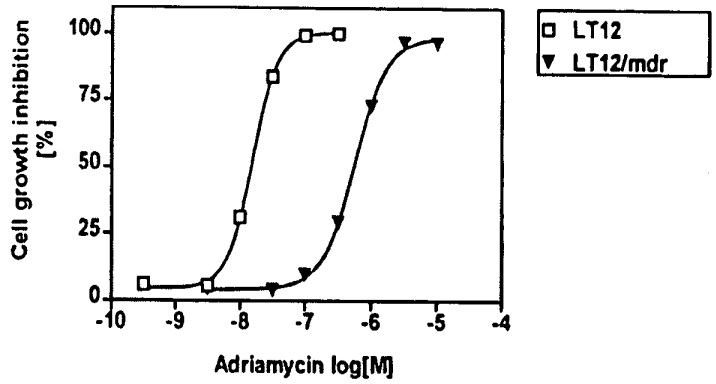
	Dose (mg/kg)	L1210 ILS %	L1210/VCR ILS %
D-24851	4 x 100 p.o.	46	42
	4 x 147 p.o.	94	85
Adriamycin	4 x 1 i.p.	158	6
Taxol	4 x 15 i.p.	82	6
Vincristine	4 x 0.2 i.p.	47	-11

FIG. 3

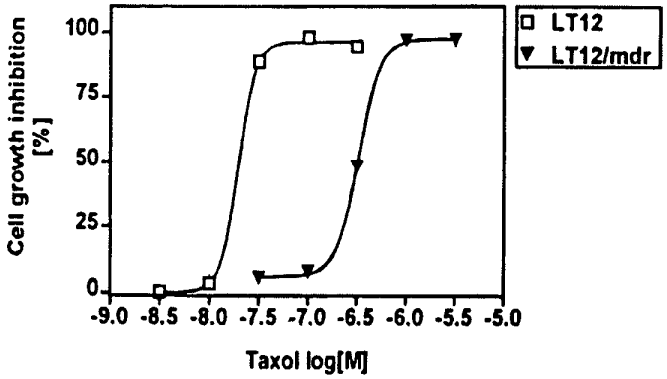
Cytotoxic activity of vincristine on a human leukemia (LT12 and LT12/mdr)



Cytotoxic activity of adriamycin (doxorubicin) on a human leukemia (LT12 and LT12/mdr)



Cytotoxic activity of Taxol on a human leukemia (LT12 and LT12/mdr)



Cytotoxic activity of D-24851 on a human leukemia (LT12 and LT12/mdr)

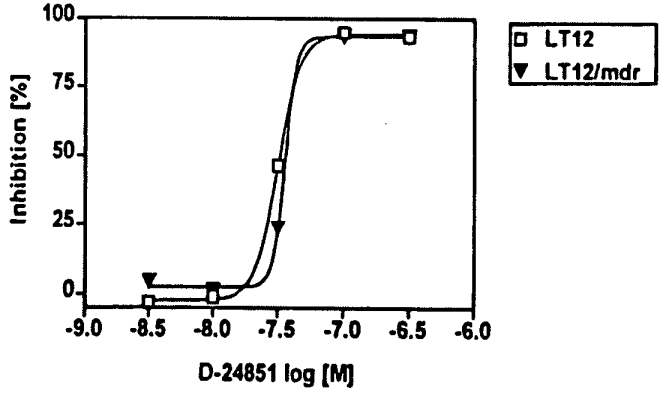
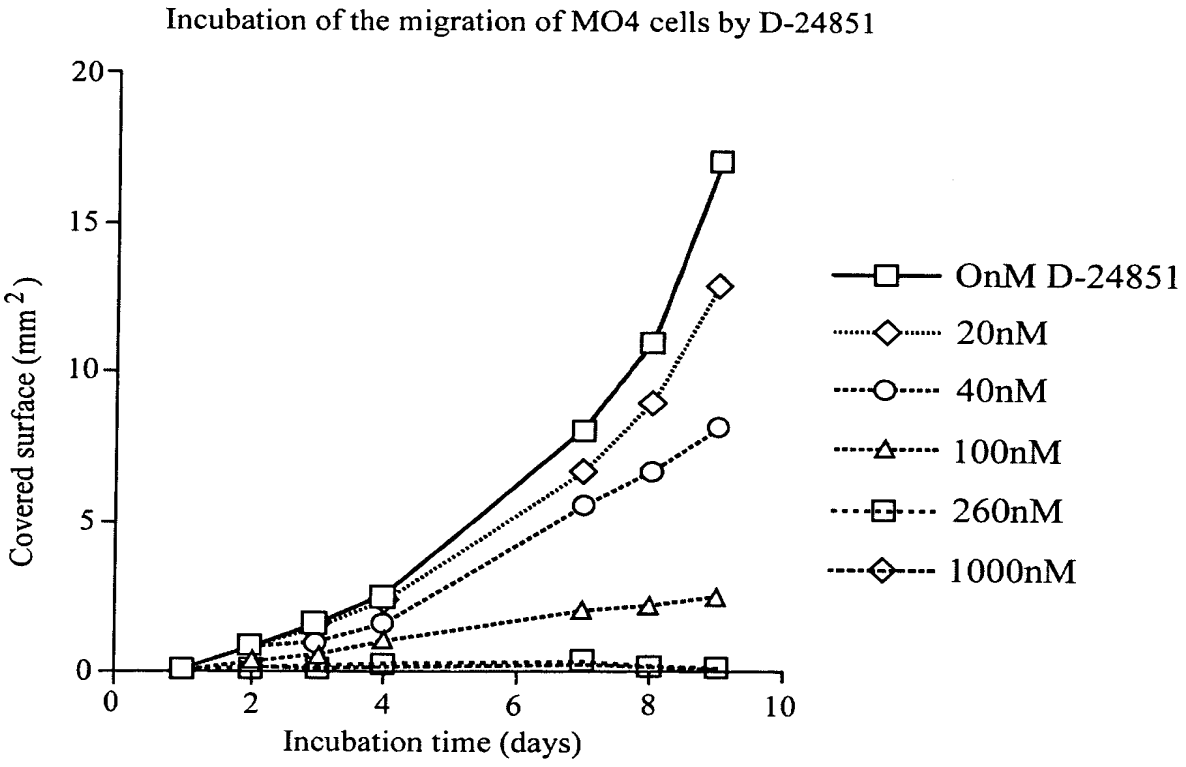


FIG. 4

FIG. 5



- D-24851 inhibits the migration of MO4 cells in a dose-dependent manner
  From this, an antiinvasive and an antimetastatic action can be derived for D-24851.

Neurotoxicity

	D-24851 10x 20 mg/kg p.o	Vincristine 10x 0.2 mg/kg i.p.	Taxol 10x 15 mg/kg i.p.
Ataxia (rat)	--	+	++
Traction (rat)	--	+	++
Reaction (rat)	--	++	+++

+ $p \geq 0.05$ vs. control ++ $p \geq 0.01$ vs. control -- = no effect

D-24851 shows no neurotoxity [sic] in maximally antitumor-active doses in contrast to Taxol and vincristine

FIG. 6

Influence of D-24851 on the nerve conduction velocity (NCV) (rat)

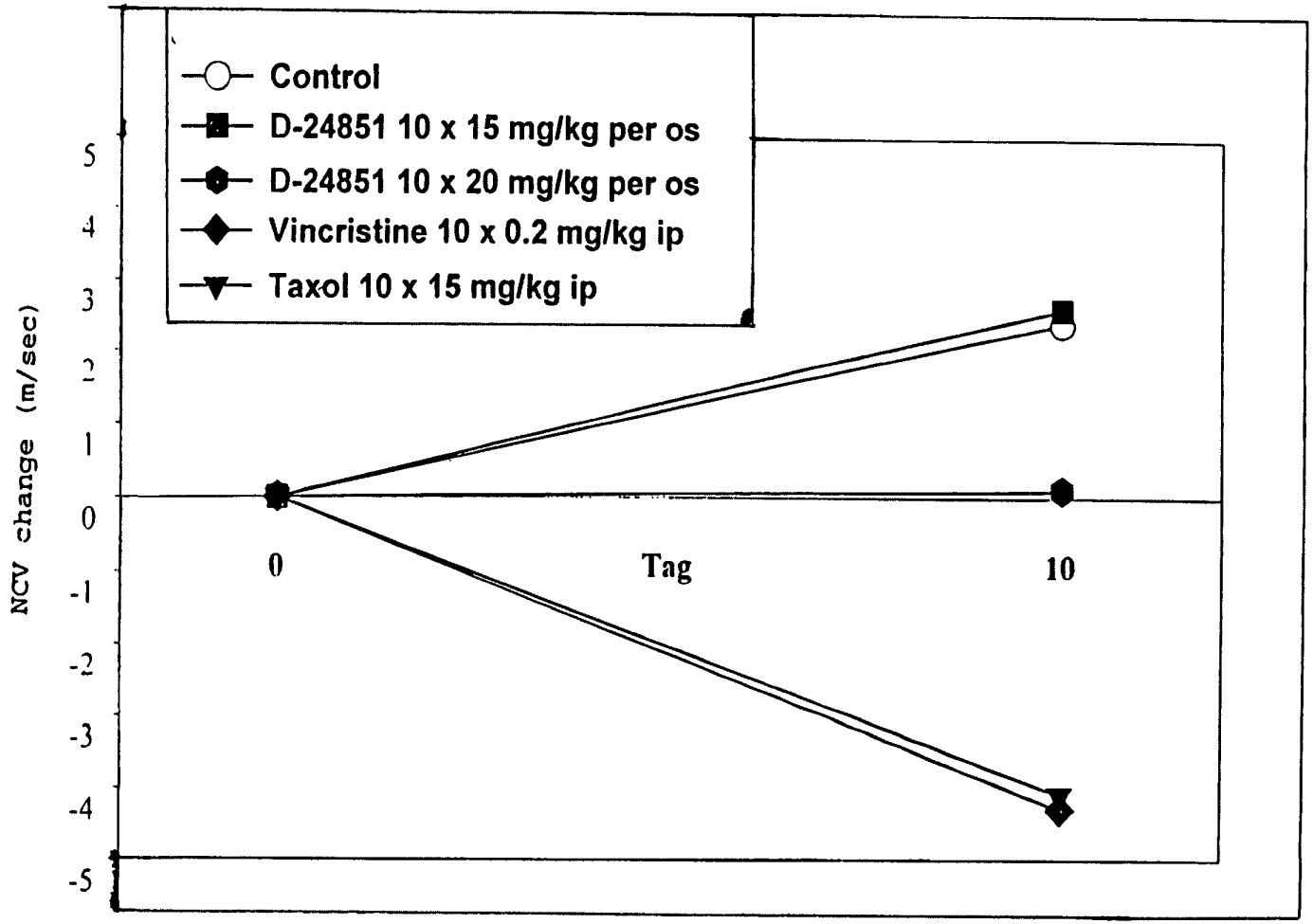
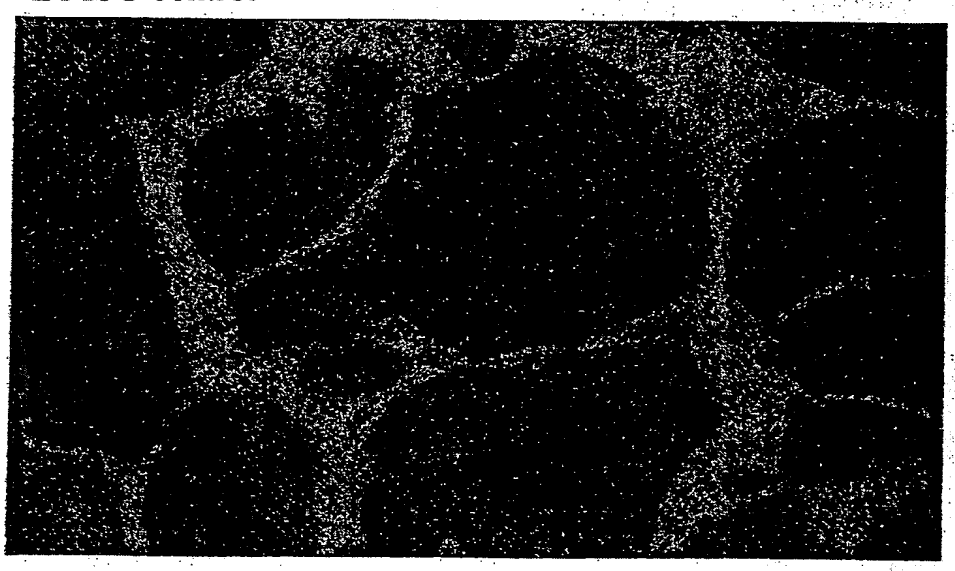


FIG. 7

FIG. 8

Angiogenesis in human endothelial cell culture
Vital staining, 44 hours after induction of angiogenesis

DMSO control



0.1 μM D24851

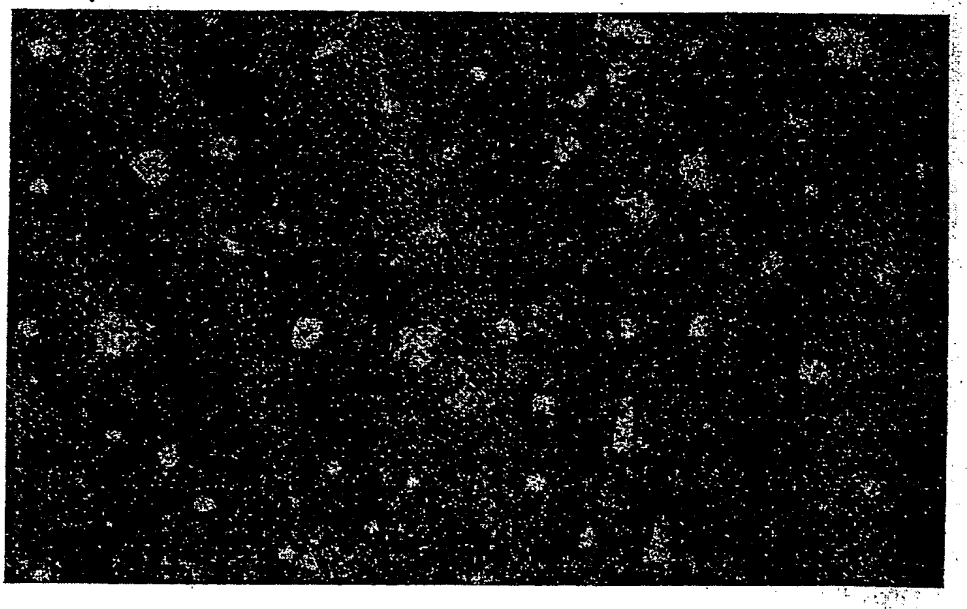
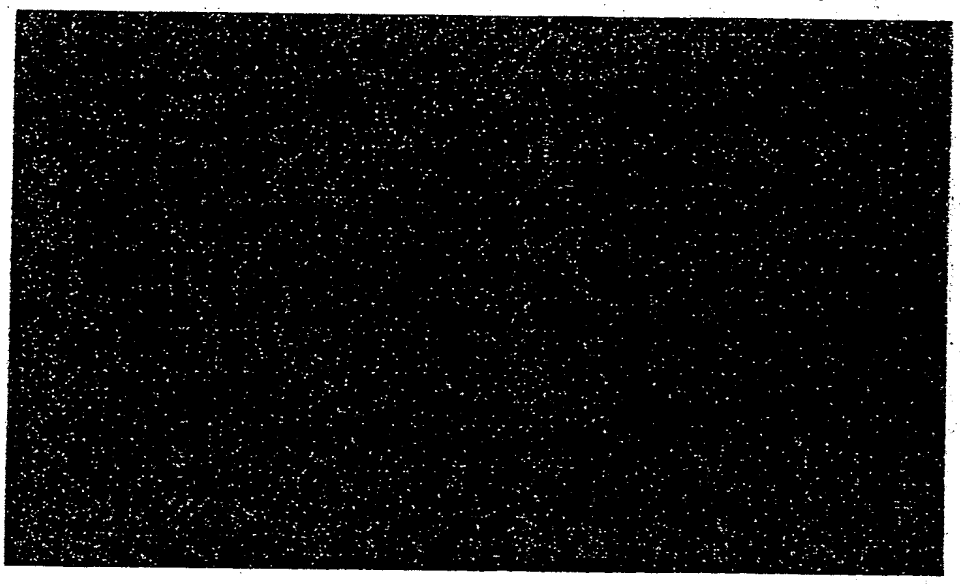


FIG. 9

Angiogenesis in human endothelial cell culture

Lethal staining, 22 hours after induction of angiogenesis

DMSO control



0.1 μM D24851